<div align="center">**REMARKS**</div>

1. Formal Matters

1.1. Sequence Listing Compliance

Applicants hereby submit the following:

a paper copy (e-filed ASCII text file) of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

the Sequence Listing in computer readable form (same file), complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein.

The description has been amended at pages 21, 22 and 24-26 to comply with §1.821(d).

The undersigned attorney or agent hereby states as follows:

(a)   this submission does not include new matter [§1.821(g)];

(b)   the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];

(c)   if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)]; and

(d)   if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)].

Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

1.2. The title has been amended to make it more descriptive.

1.3. The specification at page 6 and 21 has been amended to delete (page 6) or inactivate (page 21) the embedded hyperlinks. This satisfies the concerns expressed in MPEP 608.01.

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1.4.   The bibliography p. 45 has been amended to supply the complete citation for "Towers et al. 1999" as cited on p. 5.

1.5.   The Abstract of the Disclosure has been amended to correct "usega" to "use", and to reduce it to less than 150 words.

1.6.   The rejection is in "mark-up" form, with marginal comments which make it unclear which rejections are being made.

1.7.   Claim 4 has been amended, and claims 42-48 added, with basis at P6, L14-16; P7, L4-5; and P7, L21-35.

2.   Definiteness Issues

2.1.   Claims 6 and 9 have been amended to overcome the antecedent basis problem raised with respect to "said mutation". It is noted that base claim 4 recites a sequence "at least 94% identical to the amino acid sequence shown in SEQ ID NO:2" and which therefore may differ by mutation from SEQ ID NO:1, and clause (b) recites "said polypeptide includes at least one substitution in the VR3 region"; "substitution" is a form of mutation.

We respectfully assert that there is no antecedent basis problem for "position 212" in claim 6.   This is said to be a position in SEQ ID NO:2, and the sequence listing shows that SEQ ID NO:2 has 639 amino acids.   It is not necessary to recite that SEQ ID NO:2 "has a position 212" in order to provide antecedent basis for it.   There are thousands of issued claims in which positions in sequences are referred to without such cumbersome circumlocution.   The examiner is reminded that the goal of "antecedent basis" doctrine is to increase, not decrease, clarity.

3.   Prior Art Issues

3.1.   At the outset, Applicant wish to point out that it is unclear which rejections are being made.

It appears that the action as mailed was actually an internal draft which the Examiner's Supervisor, Bruce Campbell

(the "BC2" of the "Comment [BC1]" on page 6) has marked up or commented on.

In particular, Applicants note that the following rejections appear in right margin boxes marked "Deleted" and therefore seemingly are not in fact made:

   (1)   on page 4, the rejection of claim 1 as obvious over Towers et al. (2000), Aagaard et al. (2002), and Russell USP 5,858,753 (the rationale of this "rejection" is incomplete, the box ending with "This author... [1]" (but see page 8);

   (2)   on page 4, the rejection of claims 4, 6 and 8 as obvious over Mark and Rapp (1984) in view of Aagaard (2002) (no rationale given); and

   (3)   on page 6, the rejection of claims 4, 6, 8 as obvious over Sijts (1994) in view of Yang et al. (1999) (no rationale given) (but see page 6).

3.2. Hence, we understand the pending prior art rejections to be the following:

(I) of claims 4, 6 and 8, as <u>anticipated</u> by Mark and Rapp (1984) as evidenced by Aagaard et al. (2002) and Yang et al. (1999) (page 4);

(II) of claims 4, 6 and 8, as anticipated by Sijts et al. (1994) as evidenced by Yang et al. (1999) (page 6);

(III) of claim 1, as obvious over Towers et al. (2000), Aagaard et al. (2002) and Russell, USP 5,858,743 (page 8); and

(IV) of claims 4, 7 and 10, as anticipated by or obvious over either one of Sijts et al. (1994) or Mark and Rapp (1984).

3.3. We also understand claim 9 to have been deemed allowable if rewritten in independent form.

The Examiner asserts that (I) Mark and Rapp Fig. 7 anticipates because there is 94.2% identity between SEQ ID NO:2 and one of the sequences of Fig. 7, and (II) Sijts anticipates because there is 94.6% identity between SEQ ID NO:2 and Sijt's Fig. 3 MCF1233 sequence.

Applicants have amended claim 4 to recite at least 95%

identity, with basis at page 7, line 16.

It accordingly appears that rejections (I) and (II) are overcome.

Rejection (III) is moot because claim 1 has been cancelled.

Hence, only rejection (IV) remains to be considered. Clearly, there is no anticipation for the reasons discussed in connection with rejections (I) and (II).

With respect to obviousness, <u>Mark and Rapp (1984)</u> merely compared the predicted amino acid sequences of the pCI-3, Mo-MCF and AKV ecotropic <u>env</u> genes. They did not carry out any mutational analysis. At most, they highlight where these sequences vary. Conceivably, the Examiner's database sequence could be changed in accordance with the alternatives set forth in Fig. 7, although there is no explicit teaching to that effect and we do not concede there is motivation.

Comparing Fig. 7 with the Examiner's alignment (OA page 5), we have

Fig. 7 Position	Alternatives in Fig. 7[1]	SID2	Effect of change from DB sequence residue (underlined in col. 2) to alternative of col. 2 on # identities
59	A/V	A	-1
81	I/V	I	+1
171	D/N	S	0
213	I/T	T	-1
233	S/P	P	-1
290	D/N	N	-1
294	R/Q	Q	-1
349	E/G	E	+1
351	T/A	T	+1
353	Q/R	Q	+1

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[1] The underlined residue is the one appearing in the database sequence of the examiner's alignment.

| 602 | W̲/C | C | +1 |
| 634 | G̲/E | E | +1 |

Thus, there are six potential substitutions which increase identity with SEQ ID NO:2, five which decrease it, and two which have no effect.

There is no teaching in Mark and Rapp which favors the ones which increase resemblance to SEQ ID NO:2 over those which decrease that resemblance. If all of the substitutions were made, the net effect would be to increase the identity to SEQ ID NO:2 by 1. Since SEQ ID NO:2 is 639 a.a., this would increase the % identity by 1/639, which is less than 0.2%. A 0.2% increase from the starting alignment of 94.2% still would not reach the claimed 95%.

Mark and Rapp also indicate that Clone pCI-4 differs from the "master" sequence of Fig. 7 by a large deletion (note DEL boxes). Implementing this deletion would reduce the % identity with SEQ ID NO:2.

Si̲j̲ts likewise did not engage in any mutational analysis, merely comparing MCF1233, AKV, MCF247 and Moloney MuLV (COL) ENV proteins in Fig. 3 (p. 346). The MCF1233 sequence could conceivably be altered to the alternative residues of the three other sequences, although this is not explicitly taught and we do not concede motivation.

Plainly, some of the "alternatives" shown in Fig. 3 would actually reduce the % identity with Fig. 3. For example, MCF1233 has G3, same as SEQ ID NO:2. If this were replaced with S(AKV) or R(MOL), % identity would be diminished. The same is true of positions 4-6.

The number of alternatives exhibited in this comparison is too high for a complete analysis like that of Mark and Rapp above to be economical. We think it nonetheless clear that the "guidance" provided by the alternative Fig. 3 sequences will not plainly lead the skilled worker to mutate Sijts' MCF1233 in the direction of increased identity with SEQ ID NO:2, and in particular to progress in that direction sufficiently to achieve

the claimed 95% identity.   (The Examiner asserts that there is 94.6% identity, which implies 604 or 605 identities.   95% identity would require 607 identities.)

3.4. Moreover, besides requiring at least 95% identity with SEQ ID NO:2, claim 4 requires that the polypeptide is

a) capable of mediating infection of a cell by use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse for entry and unable of mediating infection of a cell by use of a human polytropic/xenotropic receptor encoded by the human RMC1 locus or

b) capable of mediating infection of a human cell....

The Examiner refers to Towers et al. 2000, Aagaard et al. 2002, Mark & Rapp 1984 , Sijts et al. 1994, Yang et al. 1999 and Russell US Patent 5858743 as basis for various rejections under 35 USC § 102 and/or 35 USC § 103. However, the viruses of the prior art documents do not disclose a purified retroviral envelope polypeptide, capable of mediating infection of a cell by the use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse and unable to mediate infection of a cell by use of a human polytropic/xenotropic receptor encoded by the human RMC1 locus.

Applicant wishes to stress that the cited SL3-3 virus is not identical to SL3-2 of the present invention. SL3-3 uses the ecotropic receptor for entry into the host cell.

Towers et al. and Aagaard et al. both investigate the host tropism and restriction (Fv1) of ecotropic viruses that make use of the mCAT1 receptor for entry into the host cell. Thus, the viruses studied and disclosed in Towers et al. and Aagaard et al. are not within the scope of the present invention, as the purified envelope polypeptides according to the present invention relates uses the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse. In Towers et al. the viruses are pseudotyped with the Vesicular Stomatitis Virus G (VSV-G)- envelope polypeptide, which makes use of the VSV-G pantropic receptor.

Yang et al describe the cloning of the Rmc1 gene that encodes the receptor for polytropic/xenotropic viruses. Yang et al. does not disclose a retroviral envelope but its receptor. Examiner refers to page 217 and states that human cells are permissive to MCF virus. Reading on to page 218, lines 4-10, Yang specifically describes that the human SYG1 expression (corresponding to the human RMC1 locus) is sufficient for infection by MCF.

Consequently, Yang et al. is not relevant for discussing novelty and obviousness of the present invention as the reference does not disclose a purified retroviral envelope polypeptide capable of mediating infection of a cell by use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse for entry and unable to mediate infection of a cell by use of the human polytropic/xenotropic receptor encoded by the human RMC1 locus.

Mark & Rapp describes an isolate of mink cell focus forming murine leukemia virus (MCF- MuLV) that is a recombinant between ecotropic and endogenous xenotropic related MuLV sequences. The nucleotide sequence of the prp15E protein of the isolate reveals only 1% divergence from the AKR-MuLV ecotropic sequence (P. 532). Consequently the isolate is not capable of mediating infection of a cell by the use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse and unable to mediate infection of a cell by use of a human polytropic/xenotropic receptor encoded by the human RMC1 locus.

Sijts et al. disclose an MCF 1233 isolate which according to figure 1 has an ecotropic and polytropic envelope. Consequently the MCF1233 is not capable of mediating infection of a cell by the use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse and unable to mediate infection of a cell by use of a human polytropic/xenotropic receptor encoded by the human RMC1 locus.

The examiner cites paragraphs 6 and 8 of Russell. In paragraph 6, the well known mechanism for receptor-mediated

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fusion of a retroviral envelope (glycoprotein) and a target cell membrane is described. Paragraph 8 describes that Moloney MLV is an ecotropic virus and consequently is not capable of mediating infection of a cell by the use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse and unable to mediate infection of a cell by use of a human polytropic/xenotropic receptor encoded by the human RMC1 locus.

The various viruses and the receptor used for entry into the host cell are listed below in the table.

Document	Examples of viruses	Receptor for entry
Present invention	SL3-2	Rmc1 locus of the NIH Swiss inbred NFS/N mouse
Towers et al. 2000	Viruses derived from LNCX vectors from Clontech (i.e. constructs harboring elements from Moloney Murine Leukemia virus and murine sarcoma virus pseudotyped with VSV-G (enveloped by the use of the envelope protein G of VSV	VSV-G pantropic receptor
Aagaard et al. 2002	Akv MLV, SL3-3 (ecotropic)	mCAT1 (see for example abstract, p 439 last paragraph)
Mark and Rapp 1984	pCI-3, Mo-MCF, Akv MLV (ecotropic)	mCAT1
Sijts et al. 1994	MCF 1233 (ecotropic/polytropic?)	
Russell et al.	Moloney MLV (ecotropic)	mCAT1

Thus, the present invention of a retroviral envelope polypeptide capable of mediating infection of a cell by the use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse and unable to mediate infection of a cell by use of a human polytropic/xenotropic

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receptor encoded by the human RMC1 locus is not obvious.

      3.5.   Finally, claim 4 requires that the "polypeptide includes at least one substitution in the variable region 3 (VR3) region, defined by Fig. 2 as AAs 199-213 of SEQ ID NO:2. None of the references make it obvious to alter the tropism by a substitution in this region.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By:
          Iver P. Cooper
          Reg. No. 28,005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\g-i\hoib\PEDERSEN10\pedersen10.pto amend.wpd